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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,127	09/18/2000	Wolfgang H. Dillmann	220002057202	9042

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 10/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/664,127	Dillmann et al.
Examiner	**Art Unit**
Shin-Lin Chen	1633

-- The MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Jul 23, 2002*

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-32* is/are pending in the applica

4a) Of the above, claim(s) *10-20* is/are withdrawn from considera

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-5, 7-9, and 21-32* is/are rejected.

7) [X] Claim(s) *6* is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirem

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

Applicants' amendment and declaration filed 7-23-02 has been entered. Claims 1, 2 and 5 have been amended. Claims 21-32 have been added. Claims 1-32 are pending and claims 1-9 and 21-32 are under consideration.

1. Applicant's election with traverse of group I, claims 1-9, in Paper No. 3 is acknowledged. The ground of traversal and examiner's response to the arguments are as discussed in the preceding Official action mailed 1-31-02 (Paper No. 5).

2. Claims 10-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 3.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 25 recites the limitation "The method of claim 1" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 is directed to a vector.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The 35 U.S.C. 112 first paragraph rejection has been withdrawn since an adenoviral vector can be used to produce a recombinant protein *in vitro*.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4 and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mestril et al., 1994 (J. Clin. Invest., Vol. 93, p. 759-767) in view of Giordano et al., 1993 (Circulation, Vol. 88, p. I-139) and Hayden et al., 1997 (US Patent No. 5,658,729).

Claims 1-4 are directed to an isolated recombinant adenoviral vector comprising an adenoviral genome lacking E1A/E1B genes, a transgene coding for a heat shock protein, and a promoter operably linked to said transgene. Claim 2 specifies the heat shock protein is HSP70i, HSP27, HSP40, or HSP60. Claims 3 and 4 specify the promoter is a CMV promoter or a ventricular myocyte-specific promoter. Claims 25-32 are directed to a host cell or a recombinant adenoviral particle comprising the adenoviral vector of claim 1, and a composition comprising said adenoviral vector or particle and further comprising a pharmaceutically acceptable carrier.

Mestril teaches "Myocardial ischemia markedly increases the expression of several members of the stress/heat shock protein (HSP) family, especially the inducible HSP70 isoforms" and constructs a plasmid vector pSVTK-human HSP70 expressing human HSP70 under the control of TK promoter and the SV40 enhancer. Mestril transfected rat embryonic heart-derived myogenic cell line H9c2(2-1) with the vector set forth above and generates stably transfected cell lines overexpressing the human HSP70, and shows the transfected cell lines are significantly more resistant to an ischemic-like stress than control myogenic cells (abstract, p. 760, left column).

Mestril does not teach using replication-deficient adenoviral vector lacing E1A/E1B genes and the use of CMV promoter or myocyte-specific promoter, an adenoviral particle having the adenoviral vector and a composition comprising said adenoviral vector.

Giordano teaches recombinant replication deficient adenoviral vector is an effective vector for delivery of foreign or endogenous genes to myocardium and endothelium.

Hayden teaches preparation of a replication-deficient recombinant adenoviral vector lacking E1 or E3 genes and expressing lipoprotein lipase (LPL), and use of said adenoviral vector in gene therapy for treating LPL deficiencies. Hayden also teaches using RSV promoter or CMV promoter for the expression LPL gene product and suggest using a muscle-specific promoter in place of CMV promoter for the purpose of tissue-specific expression of gene of interest (e.g. column 1, 8). Hayden also teaches preparation of incompetent adenovirus (E1A deletion mutant) by using 293 cells infected by adenoviral vector and recovering of recombinant adenovirus by double CsCl centrifugations (e.g. column 10).

It would have been obvious for one of ordinary skill at the time of the invention to substitute the plasmid as taught by Mestril with replication deficient adenoviral vector, such as an adenoviral vector lacking E1 genes, as taught by Giordano and Hayden because Giordano teaches recombinant replication deficient adenoviral vector is an effective vector for delivery of foreign or endogenous genes to myocardium and endothelium. The buffer solution containing adenovirus is considered a pharmaceutically acceptable carrier.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to transfect rat embryonic heart-derived myogenic cell line H9c2(2-1) with a replication-deficient adenovrial vector expressing HSP70 under the control of CMV promoter and generate stably transfected cell lines overexpressing the human HSP70, and determine whether the transfected cell lines are significantly more resistant to an ischemic-like stress than control myogenic cells, or to generate an adenoviral particle comprising said adenoviral vector as taught by Mestril, Giordano and Hayden with reasonable expectation of success.

8. Claims 1, 5, 7-9, and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mestril et al., 1994 (J. Clin. Invest., Vol. 93, p. 759-767) in view of Giordano et al., 1993 (Circulation, Vol. 88, p. I-139) and Hayden et al., 1997 (US Patent No. 5,658,729) as applied to claims 1-4 and 25-32 above, and further in view of McGrory et al., 1988 (Virology, Vol. 163, p. 614-617).

Claims 5 and 7-9 are directed to a method of producing an isolated and purified recombinant vector of claim 1 by cloning a transgene coding for a stress related factor, such as HSP70i, HSP27, HSP40, or HSP60, into a plasmid containing a promoter, a polylinker flanked by left end of adenoviral 5 genome lacking E1A/E1B genes, co-transfecting said plasmid into mammalian cells transformed with the E1A/E1B genes with a plasmid containing the entire human adenoviral 5 genome with an insert making the plasmid too large to be encapsulated, and creating a recombinant genome containing the transgene without the E1A and E1B genes. Claim

7 specifies treating cell supernatant with proteinase K, followed by pheno/chloroform extraction and ethanol precipitation and identification via PCR amplification. Claim 8 specifies purifying the recombinant vectors by double CsCl gradient ultracentrifugation. Claims 21-25 are directed to a method of producing a recombinant replication-deficient adenoviral vector expressing a stress related factor by propagating a replication-deficient adenoviral vector in a mammalian cell transformed with adenovirus E1A/E1B genes.

The collective teachings of Mestril et al., Giordano et al., and Hayden et al. are as discussed in the previous section.

McGrory teaches construction of a plasmid, PJM17, containing the entire Ad5 DNA molecule, with an insert in the E1 region that exceeds the packaging constraints of the adenoviral capsid, and co-transfecting 293 cells, which expresses E1A and E1B, with said PJM17 plasmid and an E1-containing plasmid carrying mutated sequences to produce recombinant adenovirus virions at high efficiencies. Both E1A and E1B mutants as well as foreign gene inserts in the E1 region can be rescued into virus (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to use the method taught by McGrory to prepare the recombinant adenoviral vector of claim 1 because of the reasons discussed in previous section in preparing the adenoviral vector of claim 1 and McGrory teaches a method for preparing an adenoviral vector. It would have been obvious for one of ordinary skill because it was sell known in the art to treat cell supernatant with proteinase K, followed by pheno/chloroform extraction and ethanol precipitation to prepare viral vector and

identify viral DNA via PCR amplification. It also was well known in the art to purify DNA or recombinant vectors by double CsCl gradient ultracentrifugation and Hayden also teaches using double CsCl centrifugation to recover adenoviruses.

One ordinary skill in the art at the time the invention was made would have been motivated to do so in order to prepare a replication-deficient adenoviral vector expressing HSP72 under the control of CMV promoter for transfecting rat embryonic heart-derived myogenic cell line H9c2(2-1) and generate stably transfected cell lines overexpressing the human HSP70, and determine whether the transfected cell lines are significantly more resistant to an ischemic-like stress than control myogenic cells according to the collective teachings of McGrory, Mestril, Giordano and Hayden with reasonable expectation of success.

Conclusion

9. Claims 1-5, 7-9 and 21-32 are rejected. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Shin-Lin Chen, Ph.D.